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HEPATITIS AND BLOOD TRANSFUSION

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12. Discussion

GENETIC PREDISPOSITION TO HEPATITIS

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It isn't often that an esoteric "blood group" deserves the critical scrutiny that the Australia antigen is receiving: this is obviously just a manifestation of its crucial importance in this modern era of medicine.

Dr. Blumberg indicated that he makes hypotheses because of their fruitful impact regarding further experimentation; and I think the fruitfulness of this hypothesis needs no further comment. Precisely because of the importance of this area, one is obliged to remark that there are still many open questions about the genetic foundations of the transmission of the Australia antigen.

Now, no one can doubt the general principle that genetic factors are likely to influence predispostion or susceptibility to viral infection. In the present context, e.g., the role of Trisomy 21 in making susceptibility almost inevitable is very well documented. The question is whether the factor that appeared in the families that Dr. Blumberg and Dr. Ceppellini have published do represent the segregation of a simple inherited gene or whether other hypotheses are still equally tenable.

Nothing that has been presented so far is incompatible with a simple genic determination. That is not necessarily saying very much because as soon as you introduce variable penetrance (and the necessary concomitants of other factors--exposure to viruses, and so forth) you might reconcile any volume of data with "a simple genetic hypothesis".

As Dr. Blumberg has pointed out, one crucial contradiction to the hypothesis would be the failure of Au(1) to cluster in families. This is contra factual in that the disease is clustered in families.

I don't think it helps very much to bring in hypothetical polygenic factors. The data should, of course, be scrutinized very carefully to be sure that the apparently discontinuous occurrence of the Australia antigen factor is not a threshold artefact of our assay methods. But a single recessive gene for susceptibility works out as well as any other genetic hypothesis.

This situation is typical of many nurture/nature paradoxes and problems in man, and they are very, very difficult to resolve. In some respects, this one is more sharply focused than the question of nature -vs- nurture influence on such developmental outcomes as intelligence, because we are presented with what appears to be a discontinuous distribution of a biochemically assayable product.

One would like to know the outcome if the level of the postulated gene product could be quantitatively measured over a wider dose range of infective unit particles. Our present assay methods do not enable us to reach that far into subclinical manifestation of viremia which may still be important in the transmission of the disease without being accessible to immunological tests.

The alternative hypothesis is, of course, that there is no genetic factor whatsoever in the families in Sardinia or in the South Pacific, and that the familial clustering is entirely a consequence of opportunity for the virus. It stands to reason that if a parent is excreting the virus, this will augment the chance that any of the offspring will pick it up. This seems to be favored by the greater role of the mother as a transmitter of the factor than the father, and I am left with the rather uncomfortable conclusion that I cannot reject the contradictory hypothesis; namely, that there is no gene difference whatsoever and that all of the data, all of the clustering, is due to the opportunity for environmental exposure.

It would be, then, one of those far-fetched but not impossible coincidences that the ratios that came out in the first studies happened to coincide with those of a simple data segregation. I am sure that if I had seen the data Dr. Blumberg has presented from the earlier studies, I would have reached exactly the same conclusions he did; but, on a more detailed consideration of all the data he has presented, one simply cannot decide between the extreme alternatives; namely, simple Mendelization of the gene with variable penetrance on the one hand, and variable opportunity for infection on the other. That, of course, admits many intermediary positions also.

But then we have to ask, "What can we do next, if that ambiguity is still unresolved?" And I guess the only technique that I can suggest (from the tradition of nature/nurture research) would be the examination of adoptions. If the early family environment is the mechanism for transmission of the antigen to the offspring, then in situations where there have been early adoptions, one might expect to find an incidence of the antigen which follows the characteristics of the adopted parents to a much greater degree than those of the biological parents in question.

Thus, if it were possible to find circumstances where illegitimacy were assured, it seems to me this might be one of the most promising methods of analysis one could chose. Failing such studies to give a sharp confrontation between the chromosome -vs- the virus-contaminated environment as the nexus of transmission, there is very little that we can do to prove either conclusion.

Another possible approach would be the demonstration of a clear-cut genetic linkage. That is to say, if we could establish a correlation in the transmission of the antigen with a genetic marker segregating in a kindred, we would then be in a very much stronger position than we are today.

This is still difficult. It would be greatly simplified if we had a clear-cut manifestation of the Australia antigen factor in cell culture, because we could then take advantage of the newly developed, very elegant techniques of cell fusion for demonstration of linkage of genetic factors in man. We are still some time from that.

Finally, I wish to mention the relationship of the Gm incompatibility with the hepatitis factor. The importance of this correlation in no way depends on the primary genetic hypothesis. Whether or not the Australia antigen itself is transmitted primarily by chromosomal susceptibility or through some other route, the interaction of that phenomenon with other clear-cut genetic factors like Gm is a very important aspect regarding the genetic basis of the susceptibility.

The studies that Dr. Blumberg reported are a considerable, albeit not yet conclusive, indication that Gm incompatibility protects against infection with the hepatitis virus. This is a theoretically plausible conclusion if we accept the data indicating that the hepatitis virus uses proteins from the infected cell, and from which it has departed, in building its own cell code. There are precedents, of course, for this with many other viruses.

This would suggest, then, that the likelihood of infection, when transmitted to the new host, would be diminished if the new

host were distinctive in its Gm characteristics and not tolerant to the Gm factors in the coating of the virus particle. The potential significance of such correlation is not attenuated in any way by uncertainties about the distribution of the Australia antigen itself.

Chairman, Dr. Schmid: Dr. Blumberg, would you like to respond to these two discussions?

Dr. Blumberg: I am honored to have my paper discussed by Drs. Petrakis and Lederberg. The work described in the paper which I have just presented was done in collaboration with Drs. London, Sutnick, Millman, Scott, Melartin, Coyne, Levene and others.

Dr. Ceppellini has told me that they were not able to retest the family in which both parents were Au(1). However, he has no reason to disbelieve his initial findings. The argument certainly is valid--that with the exception of Dr. Ceppellini's paper, there are no published critical matings (i.e., Au(1) x Au(1)) to test the genetic hypothesis.

I want to emphasize the point made early in the paper, that is, that one makes hypotheses to generate experiments in an attempt to disprove them. We followed this plan to test the infectious agent hypothesis. I believe this strategy has revealed many interesting aspects of Australia antigen that are not characteristic of a virus. Similarly, the genetic hypothesis was stated in the most simple and demanding form. We then designed studies that could reject it. We have not quite done that yet but the investigations have revealed characteristics of the system which are atypical for simple genetic traits. We're prepared to abandon the genetic hypothesis any time it is clearly rejected, particularly since the alternative hypotheses are likely to be even more interesting.

Now, to answer some of the other points raised by Dr. Petrakis. The postulated inherited susceptibility factor, if our views are correct, would be manifest only when people are exposed to the infectious agent. As a consequence, the Down's syndrome patients who live in large institutions where they have massive exposure, are likely to get the Australia antigen, but if they live at home or stay in small institutions where they are less likely to be exposed, they are less likely to develop chronic hepatitis with persistent Au(1). It is as a consequence of this concept that we believe that the chronic hepatitis found in the Down's syndrome children is a preventable disease. One cannot assume that all individuals admitted to an institution for the mentally retarded are bound to develop hepatitis. By the use of proper sanitation

measures in the large institutions (if this is possible), or (preferably) by maintaining the patients in small institutions, or at home, hepatitis can be prevented. It is also possible that this form of chronic hepatitis can be treated by removing the affected children to an environment where they will not be exposed as readily; and this is discussed in more detail elsewhere [55].

We have completed a family study using the complement fixation method. The complement fixation method is more sensitive than immunodiffusion, and has the advantage of providing quantitative information. These studies still must be critically reviewed and, therefore, they have not yet been published; but I can comment on them tentatively by saying that the simple genetic hypothesis using the immunodiffusion method was rejected by these findings. However, a new hypothesis which is similar to the old hypothesis was supported, namely, that the amount of persistent Australia antigen is to a large extent under genetic control. Age, sex and maternal effects are also factors in determining the amount of Australia antigen present.

The interesting study suggested by Professor Lederberg is feasible. In some primitive populations people often adopt other children, sometimes in an informal way. People who have a small number of children (or none) will adopt some from families who have many. I think that this is an excellent suggestion for a critical study.

There have been some studies on genetic linkage. As far as I know, linkage of Au(1) has not been established for any of the traits. In particular, Professor Ceppellini did not find linkage with the HLA locus.

I am pleased that Professor Lederberg emphasized the importance of the Gm association. Our finding has not been confirmed by other laboratories, but, if it is true, it means that we have a probablistic method of identifying people who are going to react in different ways to infection with Australia antigen. That means that that we may be able to determine before infection who will develop antibody, who will develop persistent antigen, and who will get acute hepatitis. I am, of course, extrapolating a great deal from the meager data, but the nature of this evidence is such that it shows how we may define the reaction that people will have to a particular infection before they get infected. If this were possible, preventive methods could be taken on a rational basis.